#80
gnd

PATENT
Our Docket: P-LA 1245

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:
Border and Ruoslahti

Serial No.: 08/349,479

Filed: December 2, 1994

For: INHIBITING TRANSFORMING GROWTH FACTOR β TO PREVENT ACCUMULATION OF EXTRACELLULAR MATRIX

Group Art Unit: 1644

Examiner: P. Gambel

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231, on February 27, 2002.

By Astrid R. Spain
Astrid R. Spain, Reg. No. 47,956

February 27, 2002
Date of Signature

Commissioner for Patents
Washington, D.C. 20231



**APPELLANTS' BRIEF PURSUANT TO 37 C.F.R. § 1.192**

Sir:

This is an appeal from the decision of the Examiner dated September 15, 2000, finally rejecting pending claims 21-23 and 25 in the above-identified patent application. A response to the final Office Action was submitted on March 15, 2001. A Notice of Appeal was timely filed on March 15, 2001, with a petition and fee for a three-month extension of time.

An Appeal Brief was due October 15, 2001, and, was timely filed on that date. The Appeal Brief filed October 15, 2001, was submitted in triplicate as required by 37 C.F.R. § 1.192(a).

On February 2, 2002, the Examiner issued an Advisory Action and Notice of Non-Compliance with 37 C.F.R. § 1.192(c), both of which assert that Applicants' after-final amendment was improperly used as a basis for new issues argued in Applicants'

Appeal Brief rendering the Brief defective under Rule 192(c). In the Advisory Action, Applicants were given a one-month time period to comply with Rule 192 (c).

In a subsequent telephonic interview with the Examiner on February 26, 2002, Applicants' representative argued and the Examiner agreed that the only issue addressed in the Appeal Brief of October 15, 2001, is priority of invention as set forth in section VI of the Brief. The Examiner further conceded that the Appeal Brief of October 15, 2001, was not defective under Rule 192(c). An Interview Summary of the February 26, 2002, telephonic interview is attached hereto as Appendix E and Applicants acknowledge the Examiner's cooperation and courtesy extended during the interview.

For the record, Applicants maintain that the after-final amendment splitting Markush-type claim 23 into two separate claims, amended claim 23 and new claim 35, each directed to a single species, does not raise new issues by introducing new claim elements or limitations. Applicants have not addressed the merits of the Examiner's argument that it is impermissible to raise new arguments on appeal and reserve the right to argue this issue on the merits in the future, if necessary. This supplemental Appeal Brief, with the exception of the foregoing remarks and the addition of Appendix E, is identical to Applicants' Appeal Brief filed October 15, 2002, which was in compliance with 37 C.F.R. § 1.192. This supplemental Appeal Brief is being submitted in triplicate.

## I. REAL PARTY IN INTEREST

The real party in interest is the La Jolla Cancer Research Foundation, now The Burnham Institute.

## II. RELATED APPEALS AND INTERFERENCES

No other appeals or interferences are known to Appellants, Appellants' representative or the assignees, which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

## III. STATUS OF CLAIMS

At the time the final Office Action was issued, claims 21-23 and 25 were pending, with claims 11 and 12 withdrawn from consideration as drawn to a non-elected invention. Claims 1-10, 13-20, 24 and 26-34 previously had been canceled. Claims 21-23 and 25 have been finally rejected. Claims 21-23 and 25 are the claims presently pending and on appeal. A copy of claims 21-23 and 25 is attached hereto as Appendix A.

## IV. STATUS OF AMENDMENTS

Appellants' response to the final Office Action filed March 15, 2001, proposed no claim amendments. The Advisory Action indicates that the proposed amendment will be entered upon filing of an appeal. Concurrently with the filing of this Appeal Brief, Appellants are filing a Supplemental Response with

proposed claim amendments. In particular, Appellants' proposed claim amendments, if entered, would result in splitting Markush-type claim 23 into two separate claims, amended claim 23 and new claim 35, each directed to a single species. Attached as Appendix B is a copy of the claims reflecting the proposed amendments.

## V. SUMMARY OF INVENTION

The invention provides a method of decreasing the deleterious accumulation of extracellular matrix (ECM) associated with a pathology or a condition characterized by the TGF-β-induced production and deleterious accumulation of extracellular matrix in a tissue by contacting the tissue with an anti-TGF-β antibody that binds to TGF-β; whereby the binding of the anti-TGF-β antibody to the TGF-β suppresses the deleterious accumulation of the TGF-β-induced extracellular matrix in the tissue (specification, page 2, lines 6-13; claims 1 and 2, as originally filed). Pathologies and conditions characterized by the TGF-β-induced production and deleterious accumulation of extracellular matrix in a tissue include, for example, glomerulonephritis, adult respiratory distress syndrome, cirrhosis of the liver and scarring (specification, page 2, lines 13-16; page 9, lines 1-6; claim 5, as originally filed).

## VI. ISSUES

Appellants traverse every ground of rejection set forth in the final rejection. The following is the issue on appeal:

1. Whether Appellants' Declaration under 37 C.F.R. § 1.131, filed on March 15, 2001, is sufficient to antedate U.S. Patent No 5,772,998 to Dasch et al.

## VII. GROUPING OF CLAIMS

Claims 21, 23 and 25, which stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Dasch et al., United States Patent No. 5,772,998 (hereinafter "Dasch et al." or "the Dasch et al. patent"), do not stand and fall together. Furthermore, claims 21 and 22, which stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Dasch et al., in view of Ruoslahti et al. (U.S. Patent 5,583,103) and/or Bassols et al., J. Biol. Chem., 263:3039-3045 (1988), do not stand and fall together.

## VIII. ARGUMENTS

The invention, as defined by independent claim 21, is directed to a method of decreasing the deleterious accumulation of extracellular matrix (ECM) associated with a pathology or a condition characterized by the TGF-β-induced production and deleterious accumulation of extracellular matrix in a tissue by contacting the tissue with an anti-TGF-β antibody that binds to TGF-β; whereby the binding of the anti-TGF-β antibody to the TGF-β suppresses the deleterious accumulation of the TGF-β-induced extracellular matrix in the tissue.

Dependent claims 22, 23, 25 and, if entered, new claim 35, are directed to the method of claim 21 and further recite the specific pathologies or conditions glomerulonephritis, adult respiratory distress syndrome, cirrhosis of the liver and scarring.

In the final Office Action, claims 21, 23 and 25 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Dasch et al. In addition, claims 21 and 22 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Dasch et al., supra, in view of Ruoslahti et al. (U.S. Patent 5,583,103) and/or Bassols et al., J. Biol. Chem., 263:3039-3045 (1988).

Appellants traverse both of the above-mentioned grounds for rejection on the basis of prior invention of the claimed subject matter vis-a-vis the effective filing date of the Dasch et al. patent. In particular, Appellants maintain that the Declaration under 37 C.F.R. § 1.131, filed on March 15, 2001, which is attached as Appendix C, sufficiently shows Appellants prior invention to antedate Dasch et al., which is attached as Appendix D.

**Regarding the Rejection under 35 U.S.C. § 102(e)**

Claims 21, 23 and 25 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Dasch et al., United States Patent No. 5,772,998.

As set forth above, claim 21 is a genus claim directed to a method of decreasing the deleterious accumulation of extracellular matrix (ECM) associated with a pathology or a condition characterized by the TGF-β-induced production and deleterious accumulation of extracellular matrix in a tissue, while claims 23, 25 and, if entered, new claim 35, are species claims that recite the specific pathologies adult respiratory distress syndrome, liver cirrhosis and scarring.

The Dasch et al. '998 patent describes a method of neutralizing the inhibitory effects of TGF-β and further references several species of pathologies, including interstitial lung fibrosis, liver cirrhosis, fibrotic skin disorders such as scleroderma and scarring. For the reasons set forth below, Appellants submit that the Rule 131 Declaration of March 15, 2001, sufficiently shows Appellants' invention of the claimed subject matter prior to the December 22, 1988, effective date of the Dasch et al. patent.

In Appellants' Declaration pursuant to 37 C.F.R. § 1.131 submitted on March 15, 2001, Drs. Border and Ruoslahti aver that they conceived, prior to December 22, 1988, the claimed methods of decreasing the TGF-β-induced production and deleterious accumulation of extracellular matrix associated with a pathology or a condition, including glomerulonephritis, adult respiratory distress syndrome, cirrhosis of the liver, and scarring, by contacting the affected tissue with an anti-TGF-β antibody.

Appellants prior Rule 131 Declaration of August 25, 1999, and accompanying exhibits were deemed insufficient to antedate the Dasch et al. The principal argument set forth in the final Office Action mailed September 15, 2001, for maintaining the anticipation rejection over Dasch et al. was the alleged lack of supporting exhibits that independently show conception of all claim elements (Paper No. 67, page 3, paragraphs 7-9; page 4, paragraph 1). In their Response to the final Office Action filed on March 15, 2001, Appellants argued that, under the controlling case law, not every claim element needs to be supported by accompanying Exhibits, provided that any missing element is supported by the Declaration itself. Furthermore, along with their Response to the Final Office Action filed March 15, 2001, Appellants submitted a further Rule 131 Declaration, which is substantially similar to the prior Rule 131 Declaration of August 1999, but contains additional specific averments with regard to the claimed species as well as a corroborating third party Declaration pursuant to 37 C.F.R. § 1.132. An Advisory Action was subsequently issued on May 14, 2001, which stated that, for the reasons of record, Appellants' submissions under Rule 131/132 and accompanying exhibits are insufficient to antedate Dasch et al. Appellants submit that the reasons of record, specifically as set forth in the final Office Action, Paper No. 67 (hereinafter "the final Office Action"), are inadequate to reject Appellants Rule 131 Declaration.

There exists no requirement to produce additional exhibits as Appellants' reliance on the averments set forth in the Rule 131 declaration itself is entirely appropriate to

establish conception of the invention prior to the effective date of the reference. In this regard, Ex Parte Ovshinsky, 10 USPQ2d 1075 (Bd. Pat. App. & Inter. 1989) indicates at page 1077:

> We point out to the Examiner that (1) all the evidence must be considered in its entirety, including the Rule 131 declarations and accompanying exhibits, records and 'notes,' (2) **an accompanying exhibit need not support all of the claimed limitations but rather a missing feature may be supplied by the Declaration itself**, and (3) it is entirely appropriate for appellants to rely on a showing of facts set forth in the Rule 131 declarations themselves to establish conception of the invention prior to the effective date of the reference. [Citation Omitted] [Emphasis Added]

The MPEP states that evidence in the form of exhibits may accompany the declaration, but does not require such extrinsic evidence (see MPEP §715.07).

While acknowledging Appellants' position with regard to the sufficiency standard for a Rule 131 Declaration at page 3, paragraph 7, of the final Office Action, the Examiner proceeded to cite Ex parte Swaney, 89 USPQ 618 (Bd. Pat. App. & Int. 1951) to nevertheless allege the insufficiency of Appellants Declaration.

On appeal, Appellants maintain that conformity with the Swaney fact pattern has not been articulated by any court in the country, including the Swaney Court itself, as the test for sufficiency of a Rule 131 Declaration and was improperly applied by the Examiner to reject Appellants Rule 131 Declaration.

The final Office Action included a discussion of the factual circumstances underlying the Swaney decision and it was argued that in Swaney the missing element that was not stated in the exhibits had apparently nevertheless been performed in the experiments described in appellants exhibits, such that there merely was a lack of mention of the performance of the missing element in the exhibits themselves (Paper No. 67, page 3, paragraph 9). The import of the Examiner's statement in this regard as well as of the remainder of the discussion regarding Swaney appeared to suggest that the Swaney facts represent the controlling legal framework for sufficiency of a Rule 131 Declaration. Appellants maintain that no court has held that in order to show conception prior to a critical date, an applicant has to provide one or more exhibits that explicitly or implicitly contain all elements of the claimed invention.

Rather, under the controlling legal standard articulated by the Ovshinsky Court "it is entirely appropriate for appellants to rely on a showing of facts set forth in the Rule 131 declarations themselves to establish conception of the invention prior to the effective date of the reference."

As set forth above, along with the Response to the Final Office Action filed on March 15, 2001, Appellants Drs. Border and Ruoslahti provided a further Rule 131 Declaration. Appellants' Rule 131 Declaration of March 15, 2001, is accompanied by Exhibits A through E. As set forth below, each of these exhibits corroborates Appellants' averments either with regard to the conception of the claimed methods prior to December 22, 1988, or Appellants' due diligence in pursuing reduction to practice of the claimed methods during the critical period.

The critical period in which diligence must be shown begins just prior to the effective date of the reference and ends with the date of a reduction to practice, either actual or constructive. Furthermore, the filing of a United States patent application represents constructive reduction to practice. 37 C.F.R. § 1.131(b).

Appellants respectfully submit that the Rule 131 Declaration of March 15, 2001, and accompanying Exhibits A through E, which are addressed in turn below, establish Appellants' conception of the claimed methods prior to December 22, 1988, as well as Appellants' diligence in the pursuit of reducing to practice the claimed methods from prior to December 22, 1988, until the filing of the priority application.

In their Rule 131 Declaration, Appellants aver that they conceived, prior to December 22, 1988, the claimed methods of decreasing the TGF-β-induced production and deleterious accumulation of extracellular matrix associated with a pathology

or a condition by contacting the affected tissue with an anti-TGF-β antibody. This averment is corroborated by the Declaration under Rule 132 by Lucia Languino, Ph.D., which was submitted as Exhibit A to Appellants' Rule 131 Declaration.

In her Rule 132 Declaration, Dr. Languino avers that she was a postdoctoral fellow in Dr. Ruoslahti's laboratory during the time period Dr. Border conducted research related to the above-identified patent application in the same laboratory. Dr. Languino further avers that, prior to December 22, 1988, Drs. Border and Ruoslahti asked her to assist in the preparation of anti-TGF-β antibodies for a stated goal of using anti-TGF-β antibodies to inhibit TGF-β in order to decrease the deleterious TGF-β-induced production and accumulation of extracellular matrix (ECM) associated with a disease, including kidney disease. Exhibit A to Dr. Languino's Declaration is a La Jolla Cancer Research Foundation "Animal Usage Form," the redacted date of which is prior to December 22, 1988, related to the project entitled "Anti-human TGF-β Cyclic Peptide," which lists Appellant Dr. Border and Dr. Languino as the investigators. Thus, Dr. Languino corroborates, based on personal observations, that Appellants, prior to December 22, 1988, conceived of using anti-TGF-β antibodies to inhibit TGF-β in order to decrease the deleterious TGF-β-induced production and accumulation of extracellular matrix (ECM) associated with a disease, including kidney disease. Therefore, Exhibit A provides independent third party corroboration by Dr. Languino with regard to the facts averred to by Appellants in their Rule 131 Declaration.

Exhibit B to Appellants' Rule 131 Declaration consists of two laboratory notebook pages from Dr. Languino's notebook that show the protocol for development of a rabbit anti-TGF-β antiserum substantially as set forth in Example III.e of Appellants' specification, and a La Jolla Cancer Research Foundation "Animal Procedure Request" form. The laboratory notebook pages from Dr. Languino's notebook have a redacted date prior to December 22, 1988, and set forth protocols for injection of rabbits with TGF-β peptides, including linear and cyclic TGF-β peptides, in order to prepare anti-TGF-β antiserum. The La Jolla Cancer Research Foundation "Animal Procedure Request" form in Exhibit B of the Rule 131 Declaration lists Appellant Dr. Ruoslahti and Dr. Languino as principal investigators and indicates the dates on which the animals were bled for anti-TGF-β serum, December 13, 16 and 21 of 1988.

As set forth above, Dr. Languino assisted Appellants in the preparation of anti-TGF-β antibodies for a stated goal of using anti-TGF-β antibodies to inhibit TGF-β in order to decrease the deleterious TGF-β-induced production and accumulation of extracellular matrix (ECM) associated with a disease, including kidney disease. The handwritten notations on the notebook page to which the "Animal Procedure Request" form is attached in Exhibit B are Dr. Languino's notations indicating that the rabbits were injected with Proteoglycan 1 (PG1), TGF-β linear peptide and TGF-β cyclized peptide. Significantly, Appellants aver in their Rule 131 Declaration that, at time the documents encompassed in Exhibit B were created, a stated goal of preparing anti-TGF-β antibodies was for their use to inhibit

TGF-β in order to decrease deleterious TGF-β-induced production and accumulation of extracellular matrix (ECM) associated with a pathology or condition, including glomerulonephritis, adult respiratory distress syndrome, cirrhosis of the liver, and scarring.

Further corroboration of Appellants conception of the claimed methods prior to December 22, 1988, is provided by Exhibit C to the Rule 131 Declaration, a conference abstract published for the Meeting of the American Society of Nephrology in San Antonio, Texas, which took place from December 11 to 14, 1988. This conference abstract, which lists Drs. Border and Ruoslahti as first and senior authors, respectively, is entitled "Transforming Growth Factor β (TGFβ) Uniquely Regulates Production of Glomerular Extracellular Matrix" and is consistent with Appellants' conception of treating pathologies related to TGF-β-mediated accumulation of extracellular matrix prior to December 22, 1988. In particular, the abstract provides evidence that Drs. Border and Ruoslahti discovered that TGF-β is unique among growth factors in its ability to stimulate ECM production, which is increased in glomerulonephritis. It is respectfully submitted that because this abstract was presented to **clinician** attendees of the Nephrology meeting, given Drs. Border and Ruoslahti's medical training, such presentation was in the context of methods of suppressing the deleterious accumulation of TGF-β-induced ECM, and not aimed merely at fulfilling the clinician attendees' academic curiosity. In this regard, Drs. Border and Ruoslahti declare in their Rule 131 Declaration that at the time this abstract was submitted, they already had

conceived of using anti-TGF-β antibodies in order to decrease deleterious TGF-β-induced production and accumulation of extracellular matrix (ECM) associated with glomerulonephritis or other pathologies associated with TGF-β-induced expansion of the ECM.

Exhibits D and E to Appellants' Rule 131 Declaration speak to Appellants' diligence in pursuing the reduction to practice of the claimed methods during the critical period. It is respectfully submitted that Exhibits D and E must be viewed in context, with Exhibit D being a grant proposal laying out experimental aims, and Exhibit E, seven months later, a publication of results obtained by performing experiments proposed in the grant proposal. Consequently, Exhibits D and E speak to Applicants' diligence not only in January and August of 1989, but also in the interim period during which the experiments were performed.

Specifically, Exhibit D consists of an excerpt from a grant application executed by Dr. Border in January of 1989 entitled "Growth Factors and Extracellular Matrix in Glomerular Disease." In the excerpt, the following goal is explicitly stated in the section entitled Specific Aims, *In vivo*:

> To develop regimens for therapeutic intervention in the disease model by antibodies and other agents capable of neutralizing the TGF-β effect.

In addition, the section related to Experimental Design and Methods, explicitly states:

> We have proposed several experiments that may provide agents that could block or ameliorate the action of TGF-β in the animal model of mesangial injury...It is conceivable that one or more of these agents could be administered to the animal and/or infused directly into the kidney as therapeutic agents to prevent the expansion of mesangial matrix...We expect that one or more of the agents to be tested will block the action of TGF-β. This information would be immediately applicable to the design of a study to treat humans with glomerulonephritis.

Thus, it is respectfully submitted that Exhibit D, at a minimum, corroborates Appellants' averments that the reduction to practice of the claimed therapeutic methods were being diligently pursued from prior to December 22, 1988, until the filing of the priority application. In addition, the content and purpose of the entire grant proposal, which includes a detailed description of Appellants' goals that are supported by extensive preliminary data, is consistent with Appellants' averments in the attached Rule 131 Declaration of conception prior to December 22, 1988.

Further with regard to Appellants' diligence during the critical time period, submitted as Exhibit E to the Rule 131 Declaration documents are excerpts of an updated draft manuscript as it existed in August of 1989, which details the results of

experiments proposed in the grant proposal. The manuscript is entitled "An Antiserum Against Transforming Growth Factor β Suppresses Experimental Glomerulonephritis" and contains the *in vivo* protocol corresponding to Example VII of the specification, directed to treatment of anti-Thy-1-induced nephritic rats with control rabbit serum or anti-TGF-β serum. In the manuscript, it is stated that the results achieved in experimental disease with anti-TGF-β treatment warrant the expectation of similar benefits for treatment of human glomerulonephritis and other fibrosis-related diseases. Appellants respectfully submit that Exhibit E provides documentation that during the critical period Appellants were diligently pursuing the reduction to practice of the claimed methods as averred in the Rule 131 Declaration. Significantly, the manuscript of August 1989 details results of the experiments proposed in the grant proposal, Exhibit D, seven months earlier such that together, Exhibits D and E speak to Applicants' diligence between January and August of 1989.

Having set forth above what Appellants believe to be shown by their Rule 131 Declaration of March 15, 2001, the issue is whether that showing is sufficient to antedate Dasch et al. In order to antedate a reference that has been cited against an application, distinct requirements exist that depend, in part, on whether the application claims a genus or species and, in part, on the species disclosed in the cited references. Consequently, claims 21-23 and 25 must be separately examined with regard to whether Appellants have made the necessary showing for prior invention of the claimed subject matter. It is for that reason, claim 21, directed to a genus, and claims 22, 23, 25 and, if

entered, claim 35, each directed to distinct species, do not stand and fall together. The analysis that follows is organized accordingly.

*Regarding Species Claims 23 and 25*

Where the claim under rejection recites a species and the reference discloses the claimed species, the rejection can be overcome under 37 C.F.R § 1.131 directly by showing prior completion of the claimed species or indirectly by a showing that the claimed species would have been an obvious modification of the species completed by applicant. In re Spiller, 500 F.2d 1170, 182 USPQ 614 (CCPA 1974).

Of the three species recited in the claims rejected as allegedly anticipated by Dasch et al., which are adult respiratory distress syndrome, cirrhosis of the liver and scarring, the Dasch et al. patent describes two species, liver cirrhosis and scarring.

With regard to the species not described in the Dasch et al. patent, which is Adult Respiratory Distress Syndrome (ARDS), Appellants respectfully submit that this species is not disclosed in the Dasch et al. patent and, therefore, is not anticipated by Dasch et al.

Based on the rule of law set forth in Spiller, Appellants can antedate the Dasch et al. patent by either showing prior completion of the species of liver cirrhosis and scarring,

or indirectly by showing that liver cirrhosis and scarring would have been an obvious modification of the species completed by applicant. Based on the standard set forth in Spiller, Appellants submit that the Rule 131 Declaration of March 15, 2001, shows prior invention of the species recited in claims 22 and 25.

With regard to showing prior completion of the species liver cirrhosis and scarring, Appellants aver to the conception, prior to December 22, 1988, and subsequent diligent reduction to practice of the claimed methods of decreasing the TGF-β-induced production and deleterious accumulation of extracellular matrix associated with a pathology or a condition, including glomerulonephritis, adult respiratory distress syndrome, cirrhosis of the liver, and scarring, by contacting the affected tissue with an anti-TGF-β antibody. Appellants averments in this regard are independently supported, for example, by Exhibit A to Appellants' Rule 131 Declaration, which is a Rule 132 Declaration by Dr. Languino, who avers that, prior to December 22, 1988, Drs. Border and Ruoslahti asked her to assist in the preparation of anti-TGF-β antibodies for a stated goal of using anti-TGF-β antibodies to inhibit TGF-β in order to decrease the deleterious TGF-β-induced production and accumulation of extracellular matrix (ECM) associated with a disease, including kidney disease. Furthermore, Exhibit C to the Rule 131 Declaration, a conference abstract published for the Meeting of the American Society of Nephrology in San Antonio, Texas, which took place from December 11 to 14, 1988, and which lists Appellants as first and senior authors, is entitled "Transforming

Growth Factor β (TGFβ) Uniquely Regulates Production of Glomerular Extracellular Matrix" and further corroborates Appellants' conception of treating pathologies related to TGFβ-mediated accumulation of extracellular matrix prior to December 22, 1988. Given that, under the controlling legal standard articulated by the Ovshinsky Court it is entirely appropriate for Appellants to rely on a averments set forth in the Rule 131 declarations themselves to establish conception of the invention prior to the effective date of the reference, Appellants submit that the combination of Appellants' averments and corroborating exhibits is sufficient to show prior conception of the claimed methods directed to species liver cirrhosis and scarring.

As set forth above, of the three species recited in the claims rejected as allegedly anticipated by Dasch et al., while the Dasch et al. describes two of the species, liver cirrhosis and scarring, it does not describe Adult Respiratory Distress Syndrome (ARDS). Appellants respectfully submit that the ARDS species is not anticipated by Dasch et al. Furthermore, Applicants submit that, for the reasons set forth above, prior conception of the claimed methods directed to species liver cirrhosis and scarring also has been shown.

*Regarding Genus Claim 21*

As set forth above, claim 21 is a genus claim directed to a method of decreasing the deleterious accumulation of extracellular matrix (ECM) associated with a pathology or a

condition characterized by the TGF-β-induced production and deleterious accumulation of extracellular matrix in a tissue.

With regard to scleroderma and interstitial lung fibrosis, the two species described in Dasch et al. that are encompassed, but not described in the above-identified application, In re Clarke, 356 F.2d 987, 148 USPQ 665 (CCPA 1966) sets forth the following:

> An applicant should not be prevented from obtaining a patent to an invention **where a compound described in a reference would have been obvious to one of ordinary skill in the art in view of what the affiant proves was completed with respect to the invention prior to the effective date of the reference.** This is **particularly true where the inventor had already appreciated that the invention was generic in nature** from his work on diverse species and was endeavoring to determine by exercise of reasonable diligence the precise scope of the invention...[A]ntedating affidavit must contain facts showing a completion of the invention commensurate with the extent the invention is shown in the reference. [Emphasis Added]

Thus, the issue is whether the species described by Dasch et al. would have been obvious to one of ordinary skill in the art in view of what the Appellants Rule 131 Declaration proves was completed with respect to the invention prior to the effective date of the reference. As stated in Clarke, one consideration in this regard is whether it can be shown that Appellants had

already appreciated that the invention was generic in nature prior to the reference date.

Appellants submit that the Rule 131 Declaration of March 15, 2001, shows Appellants' appreciation of the generic applicability of their invention to those pathologies and conditions associated with TGF-β-induced production and deleterious accumulation of extracellular matrix in a tissue. In particular, Appellants aver to the conception, prior to December 22, 1988, of the claimed methods of decreasing the TGF-β-induced production and deleterious accumulation of extracellular matrix associated with a pathology or a condition, including glomerulonephritis, adult respiratory distress syndrome, cirrhosis of the liver, and scarring, by contacting the affected tissue with an anti-TGF-β antibody. As independent corroboration of Appellants' appreciation of the generic nature of their invention, Dr. Languino avers that, based on her personal observations and communications, prior to December 22, 1988, Appellants had conceived of using anti-TGF-β antibodies to inhibit TGF-β in order to decrease the deleterious TGF-β-induced production and accumulation of extracellular matrix (ECM) associated with a disease, including kidney disease. Furthermore, Appellants published a conference abstract entitled "Transforming Growth Factor-β (TGF-β) Uniquely Regulates Production of Glomerular Extracellular Matrix" at the Meeting of the American Society of Nephrology in San Antonio, Texas, which took place from December 11 to 14, 1988. The conference abstract corroborates Appellants' appreciation, prior to December 22, 1988, that "TGF-β is unique among growth factors in its

metabolic effect on glomerular ECM" and that the release of TGF-β in glomerulonephritis could stimulate the expansion of ECM and progression to glomerulosclerosis. In this regard, Appellants aver that, at the time this abstract was submitted, they already had conceived of using anti-TGF-β antibodies in order to decrease deleterious TGF-β-induced production and accumulation of extracellular matrix (ECM) associated with glomerulonephritis or other pathologies associated with TGF-β-induced expansion of the ECM. Thus, Appellants Rule 131 Declaration and accompanying exhibits show that Appellants, prior to December 22, 1988, had conceived of the generic applicability of their invention.

With regard to the two conditions not explicitly described in the specification, but mentioned in Dasch et al., scleroderma and interstitial lung fibrosis, it is submitted that these conditions are obvious in view of what had been conceived, prior to December 22, 1988, by Appellants. In particular, as set forth herein, Appellants already had conceived of the claimed methods of decreasing the TGF-β-induced production and deleterious accumulation of extracellular matrix associated with a pathology or a condition, including glomerulonephritis, adult respiratory distress syndrome, cirrhosis of the liver, and scarring, by contacting the affected tissue with an anti-TGF-β antibody. As indicated in Dasch et al., at column 5, scleroderma, like scarring, which is disclosed in the above-identified specification, was known to be a fibrotic disease of the skin. Similarly, as is evident from the name, interstitial lung fibrosis, like Adult Respiratory Distress Syndrome, which is disclosed in the above-identified specification, was known to be

fibrotic disorder of the lung. As stated in In re Schaub, 537 F.2d 509, 190 USPQ 324 (CCPA 1976), it is not necessary for the affidavit evidence to show that applicant viewed his or her invention as encompassing more than the species actually made:

> Such a showing is unnecessary when it is otherwise established that the facts set out in the affidavit are such as 'would persuade one of ordinary skill in the art to a reasonable certainty that the applicant possessed so much of the invention as to encompass the reference disclosure.

Appellants respectfully submit that given their prior conception of the generic method of decreasing the TGF-β-induced production and deleterious accumulation of extracellular matrix associated with a pathology or a condition, including specific fibrotic disorders such as glomerulonephritis, adult respiratory distress syndrome, cirrhosis of the liver, and scarring, by contacting the affected tissue with an anti-TGF-β antibody, Appellants possessed so much of the invention as to encompass the Dasch et al. patent.

For the reasons set forth above, Appellants submit that the Rule 131 Declaration of March 15, 2001, is sufficient to antedate Dasch et al. and, therefore, that the rejection of claims 21, 23 and 25 under 35 U.S.C. § 102(e) as allegedly anticipated by Dasch et al., United States Patent No. 5,772,998, should be removed.

**Regarding the Rejection under 35 U.S.C. §103(a)**

Claims 21 and 22 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Dasch et al., in view of Ruoslahti et al. (U.S. Patent 5,583,103) and/or Bassols et al., J. Biol. Chem., 263:3039-3045 (1988).

It is asserted that Dasch et al. disclose the use of TGF-β antibodies to neutralize the effect of TGF-β, while Ruoslahti et al. and Bassols et al. describe TGF-β-induced extracellular matrix accumulation in glomerulonephritis and regulation by TGF-β of expression of extracellular matrix components, respectively. Thus, Dasch et al. is cited as the primary reference for describing the genus of using anti-TGF-β antibodies to neutralize the effect of TGF-β.

For the reasons set forth above, Appellants submit that the Rule 131 Declaration of March 15, 2001, is sufficient to antedate Dasch et al. with regard to the genus of using anti-TGF-β antibodies to neutralize the effect of TGF-β. Without the Dasch et al. primary reference, the rejection of claims 21 and 22 under 35 U.S.C. §103(a) is unsupported and should be removed.

## IX. APPENDICES

Appendix A is a copy of pending claims 21, 22, 23 and 25, which are the subject of the present appeal.

Appendix B is a copy of the claims, as proposed to be amended, in Appellants' Supplemental Response filed concurrently with this Appeal Brief.

Appendix C is a copy of Appellants Declaration under 37 C.F.R. § 1.131, filed on March 15, 2001.

Appendix D is a copy of U.S. Patent No. 5,772,998, issued June 30, 1998, to Dasch et al.

Appendix E is a copy of the Interview Summary transmitted on February 26, 2002.

## X. CONCLUSION

Accordingly, in view of the above arguments, Appellants respectfully submit that the Declaration under 37 C.F.R. § 1.131, filed on March 15, 2001, is sufficient to antedate U.S. Patent No. 5,772,998 to Dasch et al. Appellants therefore respectfully submit that the decision of the Examiner, finally rejecting claims 21-23 and 25, should be reversed.

Respectfully submitted,

February 27, 2002
Date

Astrid R. Spain
Registration No.: 47,956
Telephone No.: (858) 535-9001
Facsimile No.: (858) 535-8949

CAMPBELL & FLORES LLP
4370 La Jolla Village Drive, 7th Floor
San Diego, California 92122